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# An ultra-sensitive method for the analysis of perfluorinated alkyl acids in drinking water using a column switching high-performance liquid chromatography tandem mass spectrometry

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ABSTRACT

In epidemiological research, it has become increasingly important to assess subjects' exposure to different classes of chemicals in multiple environmental media. It is a common practice to aliquot limited volumes of samples into smaller quantities for specific trace level chemical analyses. A novel method was developed for the determination of 14 perfluorinated alkyl acids (PFAAs) in small volumes (10 mL) of drinking water using off-line solid phase extraction (SPE) pre-treatment followed by on-line pre-concentration on a WAX column before analysis on column-switching high performance liquid chromatography tandem mass spectrometry (HPLC–MS/MS). In general, large volumes (100–1000 mL) have been used for the analysis of PFAAs in drinking water. The current method requires approximately 10 mL of drinking water concentrated by using an SPE cartridge and eluted with methanol. A large volume injection of the extract was introduced on to a column-switching HPLC–MS/MS using a mix-mode SPE column for the trace level analysis of PFAAs in water. The recoveries for most of the analytes in the fortified laboratory blanks ranged from 73 ± 14% to 128 ± 5%. The lowest concentration minimum reporting levels (LCMRL) for the 14 PFAAs ranged from 0.59 to 3.4 ng/L. The optimized method was applied to a pilot-scale analysis of a subset of drinking water samples from an epidemiological study. These samples were collected directly from the taps in the households of Ohio and Northern Kentucky, United States and the sources of drinking water samples are both surface water and ground water, and supplied by different water distribution facilities. Only five PFAAs, perfluoro-1-butanesulfonic acid (PFBS), perfluoro-1- -hexanesulfonic acid (PFHxS), perfluoro-1-octanesulfonic acid (PFOS), perfluoro-*n*-heptanoic acid (PFHpA) and perfluoro-*n*-octanoic acid (PFOA) are detected above the LCMRL values. The median concentrations of these five PFAAs detected in the samples was ≤4.1 ng/L with PFOS at 7.6 ng/L and PFOA at 10 ng/L. Concentrations of perfluoro-1-decanesulfonic acid, PFDS and other perfluoroalkyl carboxylic acids were below the LCMRL values.



## 1. Introduction

Per- and poly-fluoroalkylated acids (PFAAs), particularly long chain perfluoroalkane sulfonic acids (PFSAs) and perfluoroalkyl carboxylic acids (PFCAs) are highly persistent, bioaccumulative, and may cause potential harmful effects to humans and wildlife [1]. PFAAs are ubiquitous in the environment and commonly detected globally in human blood, different environmental matrices, such as ground water, surface water, sediments, soils, wastewater effluents and biosolids, and in biota such as fish [2–6]. These compounds may present a potential risk to humans via drinking water and to wildlife via receiving waters. Other important sources of PFAAs to the environment are the landfill leachates, airports (military and civilian), industrial operations, and fire training locations. PFAAs enter the

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groundwater and surface water from these contaminated sites and ingestion can occur to populations relying on these drinking water sources. Two PFAAs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are well-studied, globally detected, have demonstrated reproductive and developmental toxicities in laboratory animals, and have potential to cause other health effects in humans [1,7,8].

Recently in 2016, U.S. EPA's Office of Water issued a lifetime health advisory level of 70 ppt for the combined PFOA and PFOS concentration in drinking water [9]. Several states, including Minnesota, New Jersey and North Carolina, also established drinking water and ground water guidelines [10–12]. Although there is significant information available relating to the occurrence, fate, and transport of PFAAs in the environment, few drinking water monitoring studies [1,13–21] have been conducted to date. Some of these studies are focused on the sites potentially impacted by point sources. PFOA and PFOS are included in the US EPA Contaminant Candidate List 3 (CCL 3) of chemicals under consideration for future drinking water regulation in the United States [9,22]. The agency included six PFAAs – PFOS, PFOA, PFNA, PFHxS, PFHpA, and PFBS in the Unregulated Contaminant Monitoring Rule 3 (UCMR 3) [22,23] and collected nation-wide occurrence data which will be helpful in developing future regulatory decisions. In order to monitor the trace levels of PFAAs in drinking water and given the new low level drinking water advisory [9], there is a need for the sensitive and highly accurate extraction and analytical methods for the wider range of analytes.

Trace level extraction and analysis of PFAAs in complex environmental matrices is very challenging. Quantification of PFAAs in low nanogram per liter (ng/L) concentrations in drinking water typically requires large volumes (100–1000 mL) which in turn introduces more matrix interferences during analysis, and thus decreases the sensitivity of the method. This requires very laborious extraction and clean-up techniques to reduce matrix interferences [1,14,15,17–21,24]. Recently, a sufficiently sensitive standard test method using direct injection method was reported for the analysis of PFAAs in water using smaller sample volume [25]. Collecting and handling such large volume of samples during the sampling campaigns and shipping to the respective laboratories is a very strenuous and expensive process. The transportation or shipment of the samples may not always be feasible due to the lack of time, distance, and in some cases, the added complication of international shipment of environmental samples. Therefore, a method developed for the extraction and analysis of PFAAs using small volumes of the sample would be both cost effective and save processing time.

Moreover, in epidemiological research, it has become more important to assess subjects' exposure to many chemicals in multiple environmental media [26]. It is a common practice to aliquot limited volumes of samples into smaller aliquots for chemical analyses. Very small volumes (<10 mL) of sample may be available for each measurement. Hence in this study, an optimized method was developed for the trace level detection of 14 PFAAs in approximately 10 mL drinking water using off-line solid phase extraction (SPE) pre-treatment followed by on-line pre-concentration on a WAX column before analysis on column-switching high performance liquid chromatography tandem mass spectrometer (HPLC–MS/MS). These PFAAs includes perfluorinated carboxylic acid chain lengths from C5–C14; and C4, C6, C8, and C10 perfluorinated sulfonates. The study demonstrates an ultra-sensitive method for the trace level analysis of 14 PFAAs using a subset of samples from a larger epidemiological study. The details on the performance characteristics that were needed for interpretation of the resulting data are presented. This pilot-scale evaluation was performed in drinking water samples using a subset of samples from the Health Outcomes and Measures of the Environment (HOME) Study, a prospective birth cohort examination conducted during 2003–2006 [27,28]. In the current study, extraction of very small volumes of drinking water to report low ng per liter (ng/L) reporting limits provides a rapid and sensitive method for the trace level analysis of PFAAs. The study demonstrates the applicability of an optimized method on drinking water samples and reports preliminary information on the quantifiable PFAAs in these archived drinking water samples collected from residents relying on different source waters (such as surface water and ground water), and water distribution facilities.

## 2. Materials and methods

Poly- and per-fluorinated alkyl acids and sulfonates mix (PFAC-MXB) contains 14 target analytes; stable isotope-labelled poly- and per-fluorinated alkyl acids and sulfonates mix (MPFAC-MXB) were used as surrogates; and sodium perfluoro-1-[$^{13}C_8$] octanesulfonate (M8PFOS) and perfluoro-n-[$^{13}C_8$] octanoic acid (M8PFOA) used as internal standards were purchased from Wellington Laboratories, Canada. A detailed list of all the chemicals, abbreviations, purities and the CAS numbers are provided in supporting information (SI) Table SI 1. Oasis HLB plus, 225 mg cartridges were purchased from Waters Corporation, Milford, MA, US. Ammonium hydroxide was purchased from Sigma Aldrich, St. Louis, MO, US and Wako Pure Chemical Industries, Ltd. Japan. Nitric acid was purchased from Fischer Scientific, Fair Lawn, NJ, US and Kanto Chemical Co. Inc., Tokyo, Japan. HPLC-grade methanol was purchased from Fischer Scientific, Fair Lawn, NJ, US and Nacalai Tesque, Inc., Kyoto, Japan. De-ionized (DI) Water (>18 MΩ cm) and methanol were pre-cleaned before use.

### 2.1. Solvent pre-cleaning

Methanol and de-ionized water used for sample preparation may contain trace amounts of PFAAs that lead to higher reporting limits. Therefore, methanol and de-ionized water are pre-cleaned by passing through Oasis WAX (2.1 × 20 mm, 30 μm) and Oasis HLB (2.1 × 20 mm, 5 μm) scrubber columns (Waters Corporation, Milford, MA), respectively. Pre-cleaned solvents are stored at room temperature in clean glass bottles capped using the aluminum foil lined cap to prevent any contamination from contact with septa or other material. All the mobile phase solvents are also pre-cleaned by connecting separate on-line scrubber columns for each mobile phase as shown in Table SI 2.

### 2.2. Sample collection for method demonstration

The samples used for demonstrating the method performance are a subset of 25 samples preserved from an epidemiological HOME Study [27]. The water samples were initially collected for lead analyses as part of the HOME Study. During 2003–2006, these drinking water samples were collected directly from the taps in participants' households in Ohio and Northern Kentucky, United States from the kitchen faucet (cold) while water running at a moderate flow rate. The tap water sample was collected immediately ('first flush sample') in a 500-mL HDPE container, leaving approximately 1/2 inch of space below the neck of the bottle to allow for the addition of the Nitric acid preservative and expansion of the water when frozen. The samples were stored in the freezer at −80 °C from the time of collection to the time of lead analyses in 2007. After the lead analyses, only 10-mL aliquots of the water samples were further preserved at −20 °C and the remaining water was discarded. The subset of water samples analyzed for the current study comprises 25 samples of 10-mL aliquots that were stored at −20 °C from 2007 to 2014 (PFAAs analyzed in 2014). Only water samples from homes

that did not filter their tap water were utilized. The sources of these drinking water samples are both surface water and groundwater.

### 2.3. Sample preparation – off-line solid-phase extraction (SPE)

#### 2.3.1. Sample extraction

Initial sample extraction was done at EPA's National Risk Management Research Laboratory (NRMRL) (Cincinnati, OH). Before loading the samples, Oasis HLB Plus (225 mg) cartridges (Waters Corporation, Milford, MA) were conditioned with 20 mL of pre-cleaned methanol and 5 mL of pre-cleaned DI water at a flow rate of approximately 10 mL/min. The actual sample volume of the drinking water samples used for method validation ranged from 4 to 12.7 mL. Therefore, all the measurements were made on weight basis and later, unit conversion was done considering density of water, 0.9976 g/mL at 73 °F ambient room temperature. Water samples were fortified with 150 μL of 0.5 pg/μL solution (75 pg) of the mass-labelled surrogate solution mix MPFAC-MXB and then loaded onto the cartridge at a flow rate of 1 drop/sec with a positive pressure pump using Sep-Pak concentrator (Waters Corporation, Milford, MA). The sample containers were then rinsed twice with 10 mL of pre-cleaned DI water and the rinsate was passed through the cartridges. Further, the cartridges are dried completely by purging with nitrogen gas (Fig. 1A flow diagram). The loaded and dried cartridges were sealed individually to avoid any possible cross contamination and held at 4 °C prior to shipment to NIES lab, Japan for elution and analysis.

#### 2.3.2. Sample elution and analysis

The dried HLB Plus cartridges along with empty original sample containers were shipped at 4 °C to the National Institute of Environmental Studies (NIES) (Tsukuba, Japan) for sample elution and analysis. As the samples used for method demonstration were archived for many years, the empty original sample containers were rinsed with 5 mL of pre-cleaned methanol to wash off any PFAAs sorbed onto the walls of the sample containers and the rinsate used to elute the target analytes from the cartridge at a flow rate of 1 mL/min. The eluate was reduced in volume to 3 mL with a centrifugal evaporator (Asahi Life Science Co., Ltd., Saitama, Japan). Finally, a 75 μL of a 10 pg/μL of internal standard solution (M8PFOA and M8PFOS) was spiked and the extract was reconstituted to 3.5 mL with pre-cleaned methanol and vortex mixed well. (Fig. 1A) The sample extracts were analyzed on the on-line-SPE-HPLC–MS/MS instrument as described in section 2.5.

### 2.4. Quality control

To monitor the background contamination, duplicate procedural blanks (pre-cleaned DI water) were spiked with the surrogates and extracted for each extraction batch. To monitor the method performance, the target PFAAs were spiked in the laboratory blanks (pre-cleaned DI water) and extracted following the method described in Section 2.3. These fortified laboratory blanks were included at both EPA and NIES laboratories. Due to the limited sample volume availability for method demonstration, the tap water samples from EPA laboratory were fortified and used as matrix fortified samples to determine the influence of sample matrix on the method performance. The tap water samples were fortified with 75 pg of target analytes and extracted following the method described in Section 2.3.

### 2.5. Instrumental analysis

Analysis of PFAAs was performed using high-performance liquid chromatograph (HPLC) consisting of LC pump, LC-30AD and binary LC pump, LC-20AB (Shimadzu Corporation, Kyoto, Japan) coupled with a triple quadrupole mass spectrometer, (LCMS-8080, Shimadzu Corporation, Kyoto, Japan). The HPLC consisted of a binary high pressure gradient pumps, column compartment, an autosampler, and high pressure switching valve. Two scrubber columns were used to pre-clean the mobile phase solvents, methanol, deionized water, and 0.1% $NH_4OH$ in pre-cleaned methanol using Oasis WAX (2.1 × 20 mm, 30 μm), Oasis HLB (2.1 × 20 mm, 5 μm) (Waters Corporation, Milford, MA) and ghost trap DS (7.6 × 30 mm) columns (Shimadzu Corporation, Kyoto, Japan), respectively (Table SI 2). A pre-concentration column, Oasis WAX column, 2.1 × 20 mm, 30 μm (Waters Corporation) was used to concentrate the large volume injection. An Inertsustain C18, 1.5 × 10 mm, 3 μm, (GL Science, Inc., Tokyo, Japan) was used as the guard column. An Inertsustain C18, 2.1 × 50 mm, 3 μm, (GL Science, Inc., Tokyo, Japan) was used for the analytical column. The LCMS was operated in the negative electro-spray ionization (ESI) mode using multiple reaction monitoring (MRM) (Table 1).

### 2.6. Stability test

The water samples were extracted at EPA lab in the USA and sample extracted cartridges were shipped to NIES lab in Japan for elution and analysis. Therefore, a stability test was conducted to check the integrity and optimum holding time of PFAAs on HLB Plus cartridges. The PFAAs fortified DI water (75 pg) was loaded onto pre-conditioned HLB Plus cartridges. After the extraction, the cartridges were dried completely by purging with nitrogen gas and stored in the refrigerator for 0, 7, 14 and 28 days until elution. All the elutions were performed on the same day to compare the recoveries of PFAAs after different holding times.

## 3. Results and discussion

### 3.1. Optimization of on-line column-switching HPLC–MS/MS using a mix-mode SPE column method

Analysis of PFAAs in drinking water was performed using on-line column-switching HPLC–MS/MS through pre-concentration. In this method, initially a large volume (3 mL) of sample extract was introduced to an on-line pre-concentration column (Oasis WAX, Waters) using a 5 mL injection loop (Fig. 1B). The large volume injections for trace level analysis of PFAAs in water improves the instrument throughput and recovery of the analysis. Prior to sample introduction, rinsing of the pre-concentration column was tested using methanol and water. When rinsed with methanol, the instrument response decreased by 30%–50% for carboxylates compared to water rinse (data not shown). Hence, the pre-concentration column was rinsed using 2 mL of DI water. During sample loading steps, an analytical column (Inertsustain C18, GL sciences) was equilibrated to initial gradient condition. Then, the pre-concentration and analytical columns were linearly connected using a six port valve and analytes were eluted off the pre-concentration column using 0.05 mL of 0.1% NH4OH in MeOH. Eluate was diluted through a mixing tee with DI water (total flow rate of 0.25 mL/min) and transferred onto an analytical column for separation and quantification (Fig. 1B). The total run time was 21 min. The complete gradient program was optimized for the pre-concentration on the WAX column and separation of all analytes and matrix interferences on the analytical column (Fig. 2). All 10 perfluorinated carboxylic acids (PFCAs) and 4 perfluorinated alkylsulfonic acids (PFSAs) were well separated (Fig. 2A and B). The mass spectrometer was operated in the multiple reaction monitoring (MRM) mode using electrospray ionization (ESI) using the conditions summarized in Table SI 2. Ionization and collision cell parameters are optimized for each individual analyte. The dwell time was set at 25 msec. Except for

**Table 1**
LC–MS/MS parameters of all target analytes, surrogates and internal standards and the LCMRL values of target analytes.
Note: LCMRL – lowest concentration minimum reporting level; RSD – relative standard deviation; SRM – single reaction monitoring; CE – collision energy; n.c. – no confirmatory transition.

| Analyte Name | Analyte Abbreviation | Retention Time (min) | LCMRL ng/L | Intra-Day Precision (%RSD) | Inter-Day Precision (%RSD) | Primary SRM Transition | | Confirmatory SRM Transition | | Surrogate SRM Transition | | Internal standard SRM Transition | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | MS/MS (m/z) | CE (V) | MS/MS (m/z) | CE (V) | MS/MS (m/z) | CE (V) | MS/MS (m/z) | CE (V) |
| Perfluoro-1-butanesulfonic acid | L-PFBS | 13.35 | 2.7 | 12.7 | 13.2 | 298.9 > 99.0 | 36 | 298.9 > 80.0 | 55 | 403.0 > 103.0 | 47 | 507.0 > 80.1 | 53 |
| Perfluoro-1-hexanesulfonic acid | L-PFHxS | 13.95 | 0.77 | 11.3 | 11.2 | 398.9 > 99.05 | 47 | 398.9 > 80.05 | 59 | 403.0 > 103.0 | 47 | 507.0 > 80.1 | 53 |
| Perfluoro-1-octanesulfonic acid | L-PFOS | 14.49 | 1.9 | 13.7 | 15.2 | 498.9 > 99.15 | 53 | 498.9 > 80.1 | 57 | 503.0 > 80.1 | 53 | 507.0 > 80.1 | 53 |
| Perfluoro-1-decanesulfonic acid | L-PFDS | 14.95 | 1.2 | 16.5 | 20.1 | 598.9 > 99.0 | 61 | 598.9 > 80.0 | 62 | 503.0 > 80.1 | 53 | 507.0 > 80.1 | 53 |
| Perfluoro-n-pentanoic acid | PFPeA | 13.29 | 3.4 | 16.3 | 20.4 | 262.7 > 219.0 | 9 | n.c. | | 217.0 > 172.0 | 12 | 421.0 > 376.0 | 12 |
| Perfluoro-n-hexanoic acid | PFHxA | 13.56 | 3.3 | 8.7 | 13.8 | 312.9 > 269.0 | 10 | 312.9 > 169.0 | 16 | 314.9 > 270.0 | 10 | 421.0 > 376.0 | 12 |
| Perfluoro-n-heptanoic acid | PFHpA | 13.88 | 0.64 | 10.8 | 18.6 | 362.9 > 169.0 | 20 | 362.9 > 319.0 | 11 | 314.9 > 270.0 | 10 | 421.0 > 376.0 | 12 |
| Perfluoro-n-octanoic acid | PFOA | 14.21 | 2.5 | 7.3 | 9.7 | 412.9 > 169.0 | 24 | 412.9 > 368.9 | 12 | 416.9 > 371.95 | 12 | 421.0 > 376.0 | 12 |
| Perfluoro-n-nonanoic acid | PFNA | 14.47 | 3.2 | 6.5 | 7.8 | 462.9 > 419.0 | 13 | 462.9 > 219.0 | 23 | 468.0 > 423.0 | 13 | 421.0 > 376.0 | 12 |
| Perfluoro-n-decanoic acid | PFDA | 14.7 | 1.0 | 6.6 | 6.8 | 512.9 > 468.9 | 13 | 512.9 > 219.05 | 20 | 514.9 > 469.9 | 13 | 421.0 > 376.0 | 12 |
| Perfluoro-n-undecanoic acid | PFUnA | 14.94 | 1.3 | 6.7 | 6.7 | 562.9 > 519.0 | 13 | 562.9 > 169.0 | 32 | 564.9 > 520.0 | 13 | 421.0 > 376.0 | 12 |
| Perfluoro-n-dodecanoic acid | PFDoA | 15.21 | 0.59 | 6.6 | 6.9 | 612.9 > 568.95 | 13 | 612.9 > 169.3 | 38 | 614.9 > 569.95 | 13 | 421.0 > 376.0 | 12 |
| Perfluoro-n-tridecanoic acid | PFTrDA | 15.47 | 1.4 | 5.8 | 7.3 | 662.9 > 618.9 | 15 | 662.9 > 169.15 | 37 | 614.9 > 569.95 | 13 | 421.0 > 376.0 | 12 |
| Perfluoro-n-tetradecanoic acid | PFTeDA | 15.72 | 1.8 | 9.7 | 14.3 | 712.9 > 668.9 | 16 | 712.9 > 169.0 | 41 | 614.9 > 569.95 | 13 | 421.0 > 376.0 | 12 |

PFPeA, all the analytes had two MS/MS transitions, one for quantitation and the other for qualification of analytes (Table 1). The MS/MS transitions monitored for mass-labelled surrogates and the internal standards are shown in Table 1.

### 3.2. Detection and quantitation

Detection of the analytes was based on the retention times and the product ion ratios from MS/MS transitions. The signal-to-noise ratio for detection of analytes was at least 10:1 with precision of ±15% and accuracy of 100% ± 20% for calibration and quality control standards. Seven-point calibration curves were produced for each analytical batch using blank DI water with varying amounts of the target PFAAs and fixed levels of isotopically labelled surrogate (MPFAC mix) solution and two internal standards (M8PFOA for perfluorocarboxylic acids and M8PFOS for perfluorosulfonic acids) such that the quantifiable range for this study was from 0.5–100 ng/L which was 1.5–300 ng on column. Perfluoroalkyl sulfonates are commercially available as salts, therefore they are stoichiometrically weight adjusted in the standards, so that measurements represent only the perfluoroalkylsulfonic acid concentration. Quantitation was performed with the Lab Solutions Lite (Version 5.60 SP1) (Shimadzu Corporation, Kyoto, Japan) using a linear or quadratic "1/x" weighted regression fit with a coefficient of correlation greater than 0.99. Quantitation of the target analytes was based on the internal calibration curves prepared by plotting the area ratio of analyte to the assigned internal standard versus the concentration. Concentration of each analyte in drinking water was calculated using the equation SI Eq-4. The reported PFAAs concentrations were not corrected based on their surrogate recoveries (SI Eq-3). Matrix spike recoveries of perfluoro-*n*-butanoic acid (PFBA) (139 ± 11) and perfluoro-*n*-hexadecanoic acid (PFHxDA) (140 ± 16) were out of acceptable range (70%–130%) and hence these analytes are monitored but not quantified in the current method. Further method optimization is required for these analytes. The Lowest Concentration Minimum Reporting Level (LCMRL) values for target analytes (Table 1) were determined using the procedure developed by the US EPA's Office of Ground Water and Drinking Water for drinking water [29]. The LCMRL for each analyte was determined as the lowest concentration of the analyte that can be reported with 99% confidence (Table 1). Briefly, DI water was fortified at seven different levels (0.075–15 pg/mL). Four replicates of each level were analyzed for each analyte. The LCMRL value for each analyte were then calculated using the LCMRL calculator [30].

### 3.3. Data quality control

The quality control and acceptance criteria are summarized in Table SI 3. Prior to the sample analysis, the initial precision and recovery (IPR) was established by analyzing seven spiked laboratory blanks with acceptable percent recoveries of 70%–130%. Calibration solutions were run at the beginning of every analytical batch to ensure instrument response. The percent relative standard deviation between four sets of calibration curves was 0.7%–17.1% (Table SI 6). Middle level calibration solutions were run after every tenth sample analyses to verify the previously established calibration curve. Deviation of each calibration verification was ≤± 20%. The intra-day precision values were in the range of 11.3% (PFHxS) to 16.5% (PFDS) for PFSAs and 5.8% (PFtriDA) to 16.3% (PFPeA) for PFCAs. The Inter-day precision values were in the range of 11.2% (PFHxS) to 20.1% (PFDS) and 6.7% (PFUnA) to 20.4% (PFPeA). Laboratory blank sample analysis was performed after every tenth sample in the sequence to check for instrument contamination. The target analytes concentration in these blank samples was below the LCMRL values for all the analytes. For each batch of sample extraction, two procedural blank samples

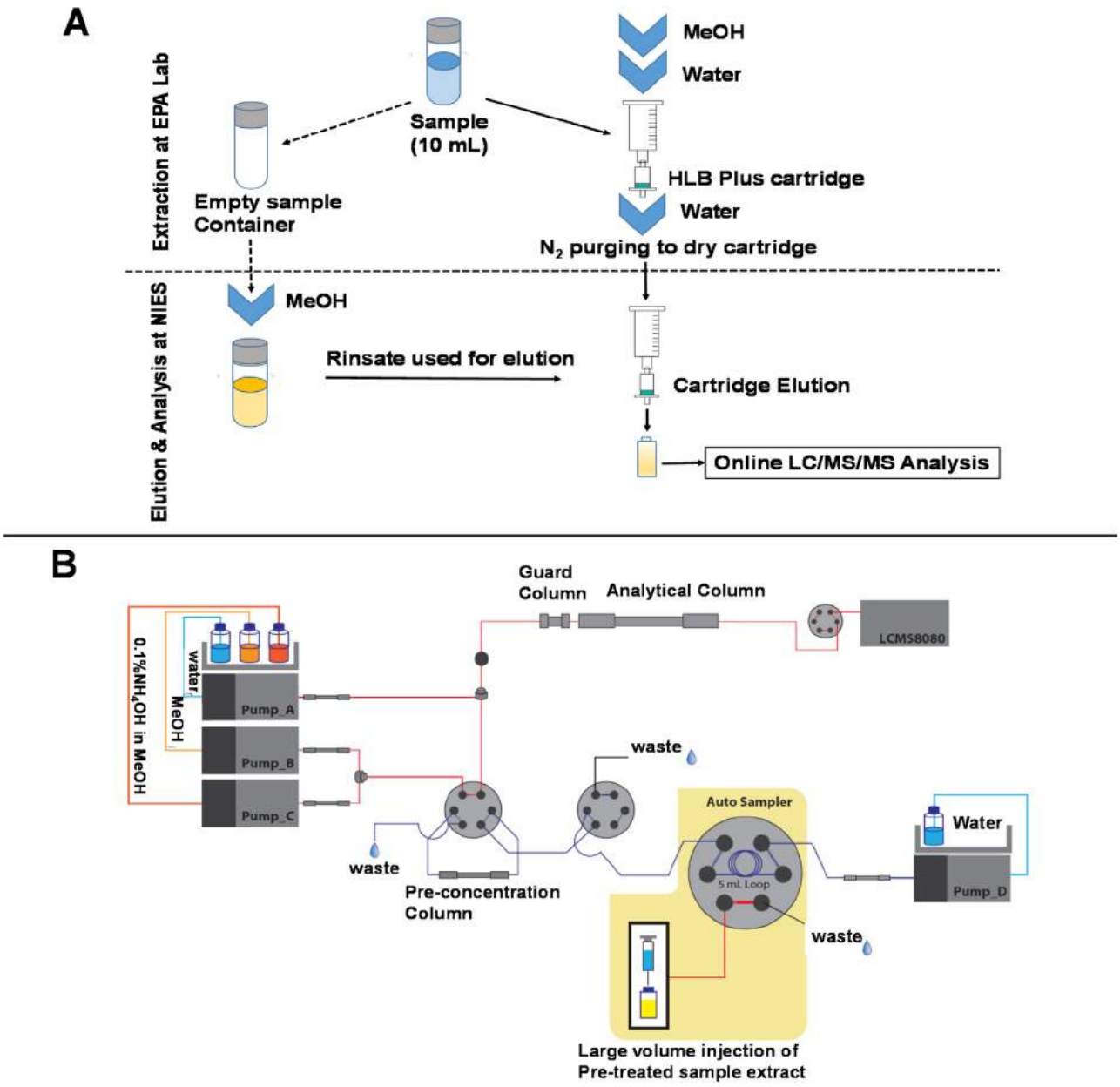


**Fig. 1.** Sample preparation and instrument analysis: (A) Extraction and elution of the sample (B) Online LC–MS/MS analysis using a mix-mode SPE column where the pre-concentration column is coupled to analytical column with a six-port valve.

(pre-cleaned DI water) were extracted to analyze for any potential contamination. These blank samples were included at both EPA and NIES laboratories. To check the Ongoing Precision and Recovery (OPR), target PFAAs were spiked into pre-cleaned DI water and extracted as laboratory fortified blanks in each batch with acceptable percent recoveries (SI Eq-1) of 70%–130% for most of the analytes and 60%–140% for PFPeA, PFHxA and PFHpA Quality control (QC) of the samples was checked by analyzing the matrix spiked samples in each batch. Matrix fortified recovery in the samples was calculated using the equation SI Eq-2. The QC samples were treated with the same procedure as the other samples and quantified by the standard curves described above. The PFAAs stability on HLB cartridges was tested to check the holding times of 0, 7, 14, and 28 days. Recovery of PFAAs concentrations between different holding times was compared using Kruskal-Wallis rank sum test followed by the Scheffe's test ($\alpha = 0.05$ as significant level) (Table SI 8). Based on this analysis, there was no significant differences among the four holding times. The data shows that PFAAs were stable on the SPE cartridges up to 28 days.

### 3.4. Quality control for method demonstration samples

Trace levels of background contamination from the extraction solvents and from the analytical instrument can contribute to the higher quantitation limits. Therefore, to improve the accuracy and the precision, pre-cleaned DI water and methanol were used. To avoid the background contamination from the analytical instrument, a separate scrubber column was used for each mobile phase to pre-clean the mobile phase solvents as mentioned above in Section 2.1. All these measures contributed to the ultra-low level detection of PFAAs in small volumes of drinking water. Isotopically-labelled surrogates were spiked in all the QC and environmental samples to account for any losses during the

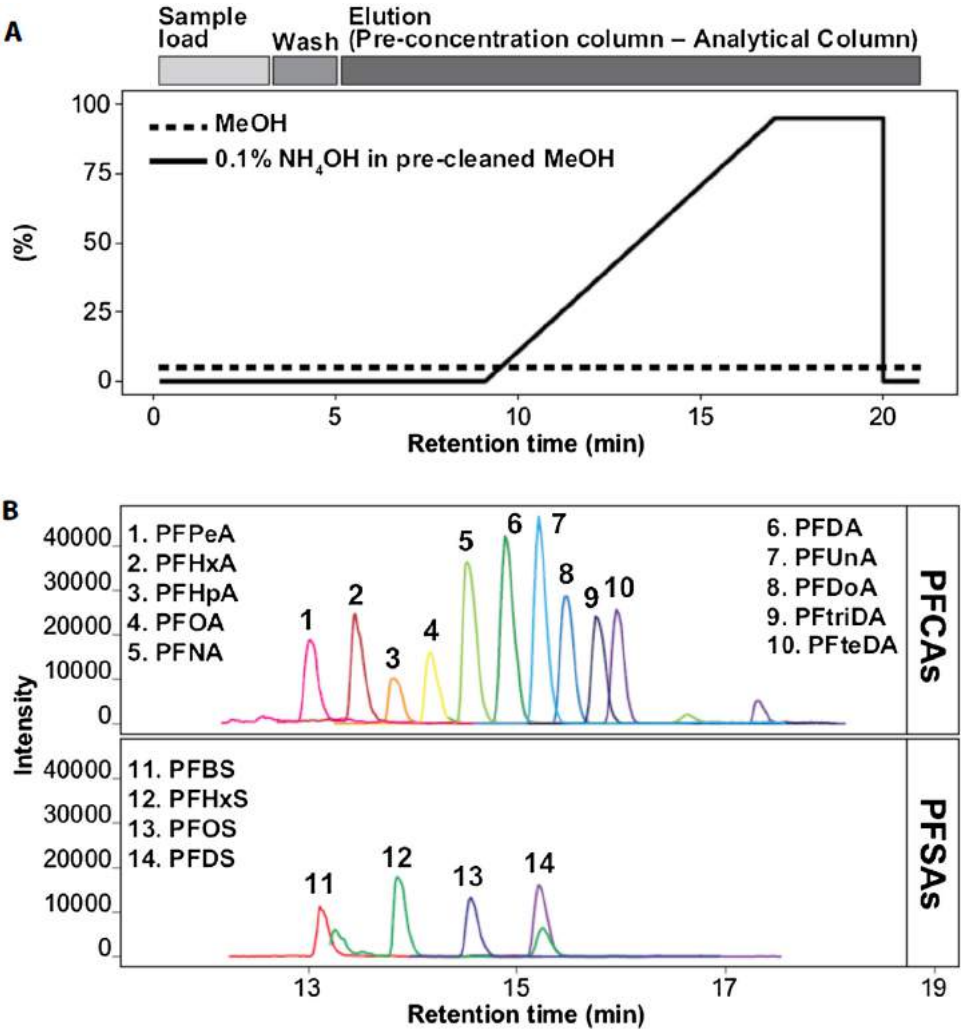


**Fig. 2.** (A) Gradient program and (B) Typical chromatogram of PFAAs (7.5 pg/mL).

sample preparation process and any differences in ionization of analytes between the standards and the extracted samples. The isotopically labelled surrogate mix contained 9 surrogate analytes (Table 1 and Table SI 1). Although exact isotope match analytes were used as surrogates for most of the analytes, the compounds for which a stable isotope labelled standard were not available, the closest chain isotope labelled standard was used for comparison. Table SI 7 shows the surrogates for the respective target analytes.

### 3.4.1. Procedural laboratory blanks

The greatest challenge associated with the trace level analysis of PFAAs is the background contamination. Therefore, duplicate procedural blanks (pre-cleaned DI water) were spiked with the surrogates and extracted for each extraction batch to analyze for background contamination in the method. The data was flagged if the analyte concentration found in the sample was at a concentration less than 5 x the level found in the procedural blank. Surrogate recoveries in the laboratory blanks were between 84%–106% with ≤ 15% RSD (Table 2). Although most of the target analytes were below the LCMRL values in the blanks processed both at EPA and NIES laboratories, there was random detection of PFHxA in one of the batch up to 1.7 times above its LCMRL value (Table SI 4).

### 3.4.2. Fortified laboratory blanks and matrix samples

For quality assurance purposes, the target PFAAs were spiked in the laboratory blanks to monitor the method performance. These fortified laboratory blanks were included at both EPA and NIES laboratories. The overall recoveries for most of the analytes in the fortified laboratory blanks (Table SI 5) ranged from 74%–114% with RSD of 7%–29%. Excellent surrogate recoveries were obtained in the fortified laboratory blanks ranging from 89%–102% with ≤14% RSD (Table 2). To determine the influence of sample matrix on the method performance, the samples were fortified with 75 pg of target analytes and extracted following the method described above in Section 2.3. Overall recoveries for most of the PFAAs from matrix fortified samples (Eq. SI-2) ranged from 73%–131% with RSD of 5%–30% (Table SI 5). Recoveries for most of the surrogates in matrix fortified samples ranged from 70%–88% with lower recoveries for some of the longer chain surrogates (Table 2). The percent recoveries were determined by fortifying the target analytes and surrogates before the extraction and accounts for any losses during the extraction procedure and handling.

## 3.5. Analysis of drinking water samples

The method performance was evaluated using 25 archived drinking water samples from the previously described HOME Study

**Table 2**
Surrogate recoveries (%) and relative standard deviations (%) in Laboratory blanks, Laboratory fortified blanks, and Laboratory fortified matrix and drinking water samples.

| | Surrogate Recovery (%) ± RSD(%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Treatments | $^{18}O_2$-PFHxS | $^{13}C_4$-PFOS | $^{13}C_2$-PFHxA | $^{13}C_4$-PFOA | $^{13}C_5$-PFNA | $^{13}C_2$-PFDA | $^{13}C_2$-PFUnA | $^{13}C_2$-PFDoA |
| Laboratory Blanks (n = 4) | 92 ± 8 | 94 ± 4 | 96 ± 6 | 98 ± 10 | 106 ± 10 | 101 ± 7 | 94 ±8 | 84 ±15 |
| Laboratory fortified Blanks (n = 4) | 91 ± 14 | 95 ± 12 | 89 ± 7 | 101 ± 6 | 102 ± 12 | 98 ± 11 | 97 ±5 | 93 ±9 |
| Matrix fortified samples (n = 4) | 81 ± 22 | 77 ± 8 | 88 ± 8 | 87 ± 10 | 88 ± 9 | 70 ± 16 | 59 ±12 | 48 ±15 |
| Drinking water samples (n = 25) | 87 ± 15 | 89 ± 14 | 54 ± 16 | 89 ± 13 | 96 ± 21 | 89 ± 26 | 74 ±21 | 67 ±24 |

[27]. The samples were selected to cover different source waters such as surface water and ground water, and different water distribution facilities in order to evaluate the method performance. The volume of drinking water in these archived samples were variable and ranged from 4 to 12.7 mL. Therefore, all the measurements were made on weight basis. The mean surrogate recoveries for most of the isotope labelled standards in the samples ranged from 74% to 96%; however, $^{13}C_2$-PFHxA and $^{13}C_2$-PFDoA demonstrated low recoveries of 54% and 48% respectively (Table SI 7). The %RSDs for the majority of these surrogate average recoveries were below 20% despite different sources of drinking water. However, sample 25 had lower recoveries for all the surrogates indicating some loss during the sample preparation steps (Table SI 7).

### 3.5.1. Concentrations in drinking water samples

The concentrations of PFAAs detected in pilot study from the HOME drinking water samples (Eq. SI-4) are summarized in Table 3. PFOA and PFHpA were the only PFCAs quantified in 84% and 88% of the drinking water samples, respectively. All the other PFCAs were below their respective LCMRL limits. PFASs are the next most commonly detected PFAAs in the drinking water samples. The sum of all 14 PFAAs in these samples ranged from 1 to 132 ng/L and the median concentration was 14.7 ng/L. The occurrence of PFOS, PFHxS and PFBS are 36%, 44% and 16%, respectively. PFDS was below the LCMRL limit in all the samples. The median concentrations of all the five PFAAs detected was ≤4.1 ng/L with PFOS at 7.6 ng/L and PFOA at 10 ng/L. However, the peak levels of PFOA and PFOS (Table 3) were relatively high when compared with previously published data in drinking water samples [14,16–18,24]. Many studies have been conducted on the drinking water in other countries around the world. Quinones and Snyder [17] measured PFAAs in finished water from seven drinking water facilities in United States of America, ranging from <1–30 ng/L of PFOA and <1–57 ng/L of PFOS. Some of these utilities were impacted by the treated wastewater effluents. Thompson et al. [14] measured drinking water across 34 locations around Australia and found PFOA and PFOS in the range of 0–9.7 and 0–16 ng/L respectively. Eschauzier et al. [18] reported 4.7 ng/L of PFOA and 0.4 ng/L of PFOS in the tap water from Netherlands. Ullah et al. [24] measured PFAAs from tap water collected from six European countries ranging from 0.3–8.56 ng/L of PFOA and 0.39 − 8.81 ng/L of PFOS. Except for Quinones and Snyder [17] study, the concentrations reported by other studies were in the low ng/L range. In the current study, the drinking water samples collected from midwest region in United States of America, measured concentrations of PFOA range from 0.56–108 ng/L and for PFOS were <LCMRL−98.6 ng/L. Some of the samples exceeded the newly issued US EPA lifetime drinking water health advisory level of 70 ng/L for combined PFOA and PFOS concentration. It should be noted that these are archived samples collected during 2003–2006 and the recent UCMR3 [9] 2013–2015 occurrence data from the water distribution systems in these areas do not show any detections above the method reporting limits of EPA method 537 [31]. Out of the 25 samples analyzed, 11 samples showed ≥10 ng/L PFOA and in 4 samples PFOS were >10 ng/L. Although the median concentrations were within the range reported in other studies around the world, the maximum concentrations measured in the current study were relatively higher compared to the literature reported values. Such high PFC concentrations were comparable to the reported concentrations in surface water and wastewater effluent samples and drinking water treatment plants impacted by wastewater effluents [5,17] in the United States. In a drinking water utilities monitoring study in the United States, Quinones and Snyder [17] found higher levels (18 ng/L for PFOA and 57 ng/L for PFOS) of PFAAs concentrations in the utilities highly impacted by wastewater effluents compared to the low wastewater impacted utilities. Although the PFAAs levels of the raw water are not measured in the current study, the drinking water samples with high levels of PFAAs, might have been potentially impacted with either wastewater effluents or other point sources.

### 3.6. Method comparison

Various methods for PFAAs in drinking water have been reported in the literature. Those methods used different sample preparation methods using SPE cartridges (such as WAX, C8 + Quarternary amine, Pre Sep C Agri, etc) for concentration and clean up [14,15,17,21,24]. Prior to analysis, Eschauzier et al. and Takagi et al. [18,21], used GHP and cellulose filters respectively to further clean-up the sample extracts. Most of these methods used either methanol or various fractions of ammonium hydroxide in methanol as the elution solvents. Ullah et al. [24], used an organic base, 1-methyl piperdine in methanol as the elution solvent and also as the mobile phase solvent to achieve high sensitive analysis of PFAAs including perfluoroalkyl phosphonates using 500 mL of drinking water. Further, Flores et al. [32], used liquid–liquid extraction (LLE) of 200 or 100 mL drinking water using (90:10 v/v) dichloromethane/isopropyl alcohol solvent mixture and used Whatman filter paper for clean-up of the extracts. Most of these methods required 500–1000 mL of sample to measure sub to ng/L levels of PFAAs in drinking water. However, using only 10 mL of the water sample, the current method showed acceptable performance compared to the other reported studies. The optimized method performance characteristics were compared with those of other studies for PFOS and PFOA (Table 4). The current method also demonstrates the stability and integrity of the extracted analytes on the cartridges, since the samples were extracted in one laboratory and the cartridges were shipped to a second laboratory for elution and analysis in a different country.

## 4. Conclusion

The optimized method for determination of 14 PFAAs in drinking water using an off-line SPE pre-treatment and large volume injection on to an on-line pre-concentration WAX column followed by column-switching HPLC–MS/MS was sensitive and reproducible. This novel method is capable of measuring sub-ng/L levels in approximately 10 mL of sample and is believed to be the first study to report ultra-trace level concentrations of PFAAs in small volume of drinking water samples. The applicability of the method was tested on wide array of drinking water sources such as surface water and ground water and proved to be reproducible. The method developed also demonstrates the stability and integrity

**Table 3**
Concentrations of PFAAs in drinking water samples. Note: Data shown only for PFAAs detected above their LCMRL values in the samples.

| Sample Name | Sample Volume, mL | Concentration, ng/L | | | | |
|---|---|---|---|---|---|---|
| | | PFBS | PFHxS | PFOS | PFHpA | PFOA |
| Sample 1 | 7.5 | * | 4.7 | 14.4 | 2.7 | 6.6 |
| Sample 2 | 10.2 | * | * | * | 1.1 | * |
| Sample 3 | 8.5 | * | 1.1 | * | 2.6 | 108 |
| Sample 4 | 4.8 | * | * | * | * | 24.6 |
| Sample 5 | 12.7 | * | 1.4 | 4.1 | 1.6 | 73.4 |
| Sample 6 | 10.2 | * | 2.6 | 36.8 | 1.9 | 3.4 |
| Sample 7 | 11.5 | * | * | * | 1.0 | * |
| Sample 8 | 11.2 | 7.1 | 2.8 | 2.7 | 1.6 | 2.5 |
| Sample 9 | 9.1 | 5.9 | 4.6 | 98.6 | 10.0 | 12.9 |
| Sample 10 | 10.3 | * | * | * | * | * |
| Sample 11 | 10.5 | * | * | * | 1.1 | 9.8 |
| Sample 12 | 9.9 | * | 1.0 | 2.3 | 1.2 | 67.4 |
| Sample 13 | 10.0 | * | * | * | 1.3 | 13.4 |
| Sample 14 | 10.4 | * | 1.3 | 2.3 | 0.8 | 10.0 |
| Sample 15 | 4.0 | * | * | * | 2.4 | 43.2 |
| Sample 16 | 10.7 | * | * | * | 1.1 | 4.8 |
| Sample 17 | 12.1 | * | 3.2 | 7.6 | 6.6 | 5.9 |
| Sample 18 | 7.2 | 11.7 | 6.0 | * | 4.1 | 12.9 |
| Sample 19 | 10.0 | * | * | * | 1.7 | 6.1 |
| Sample 20 | 8.8 | * | * | * | 1.1 | 10.1 |
| Sample 21 | 10.8 | * | * | * | 1.2 | 10.0 |
| Sample 22 | 10.1 | * | * | * | 2.3 | 2.8 |
| Sample 23 | 9.3 | * | * | * | 4.4 | * |
| Sample 24 | 10.6 | 3.9 | 2.4 | 83.1 | * | 4.9 |
| Sample 25 | 8.3 | * | * | * | 7.8 | 5.9 |
| LCMRL, ng/L | | 2.7 | 0.77 | 1.9 | 0.64 | 2.5 |

*Concentrations <LCMRL values

**Table 4**
Comparison of method performance characteristics with the literature reported methods for PFOS and PFOA.

| Reference | Preparation Method | Sample volume (mL) | PFOS | | PFOA | |
|---|---|---|---|---|---|---|
| | | | LOD (ng/L) | LOQ (ng/L) | LOD (ng/L) | LOQ (ng/L) |
| Current Study | SPE (HLB) + (WAX) | 10 | | 1.9* | | 2.5* |
| [33] | SPE (PreSep C Agri) | 1000 | | 0.025–0.05 | | 0.05–0.1 |
| [15] | SPE (PreSep C Agri) | 1000 | 0.05 | 0.1 | 0.03 | 0.1 |
| [17] | SPE (HLB) | 1000 | | 1 | | 5 |
| [21] | SPE (Sep-Pak Plus PS-2) | 1000 | | 0.5 | | 0.7 |
| [14] | SPE (WAX) | 1000 | 0.13 | 0.66 | 0.13 | 0.5 |
| [24] | SPE (C8) | 500 | | 0.024/0.052 | | 0.091 |
| [34] | SPE (WAX) | 500 | 1.3 | 4 | 1.3 | 4 |
| [18] | SPE (WAX) | 250 | | 0.2 | | 0.8 |
| [32] | LLE | 200/1000 | | 1 | | 4.2 |

* These values are determined using LCMRL procedure.

of the extracted analytes on the cartridges, as the samples can be extracted on to the cartridges and held for up to 28 days for elution and analysis. This approach could simplify field sample collection campaigns and would be both cost effective and saves processing time, as very small sample volumes are required. This method was successfully demonstrated on 25 drinking water samples and proved to be efficient, robust and reproducible. Further, the method will be used in future studies to provide data on drinking water monitoring studies.

## Conflict of interest

The authors declare no competing financial interest.

## Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA. The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the Ministry of the Environment, Japan.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.chroma.2017.03.006.

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